UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,737	11/06/2000	Stephen Quake	020174-001810US	8821

20350 7590 06/05/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/707,737	Quake
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 13, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above, claim(s) *41-54* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ *is/are allowed.*

6) ☒ Claim(s) *1-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ *are subject to restriction and/or election requirement.*

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 13, 2003 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-11, 13-21, 26-28 and 34-40 are rejected under 35 U.S.C. 103(a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002).

Livak et al teach a method of analyzing a target polynucleotide (Abstract) comprising:

a) providing a primed target polynucleotide attached to a microfabricated synthesis channel (Abstract and Column 7, line 35 to column 8, line 12);

b) flowing a first nucleotide through the synthesis channel under conditions whereby the first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide (Figure 2A-2C and Claim 1 and Column 10, lines 27-35);

c) determining presence or absence of a signal, the presence of a signal indicating that the first nucleotide was incorporated into the primer, and hence the identity of the complementary base that served as a template in the target polynucleotide (Figure 2A-2C and Claim 1 and Column 10, lines 27-35);

d) removing or reducing the signal, if present (Figure 2A-2C and Claim 1 and Column 10, lines 27-35); and

e) repeating steps (b)-(d) with a further nucleotide, the same or different from the first nucleotide, whereby the further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer (Abstract, Column 10, lines 56-65 and Claim 1).

Livak et al teach a method wherein step comprises providing a plurality of different primed target polynucleotides attached to each different synthesis channels (Column 2, lines 35-39);

Livak et al teach a method wherein the first nucleotide and further nucleotides are labeled (Column 8, line 44 to column 9, line 17 and Claim 6).

Livak et al teach a method wherein the steps (b)-(d) are performed until the identity of each base in the target polynucleotide has been identified (Abstract and Column 10, lines 56-65).

Livak et al teach a method wherein the removing or reducing is by photobleaching and by chemical release of the label (Column 13, lines 28-31 and Column 8, line 57 to Column 9, line 17).

Livak et al teach a method wherein the label is mass-spectrometric label (Column 8, lines 51-56).

Livak et al teach a method wherein at least one of the labeled nucleotide comprises a mixture of labeled and unlabeled forms of the nucleotide (Figures 2A-3B).

Livak et al teach a method of analyzing a target polynucleotide comprising:

a) pretreating the surface of a substrate to create surface chemistry that facilitates polynucleotide attachment and sequence analysis (Column 7, line 35 to column 8, line 42);

b) providing a primed target polynucleotide attached to the surface of a substrate (Figures 3A-3B);

c) providing a labeled first nucleotides to the attached target polynucleotide under conditions whereby the labeled first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide (Figures 3A-3B and Column 10, line 66 to Column 11, line 34);

d) determining presence or absence of a signal, the presence of a signal indicating that the labeled first nucleotide was incorporated into the primer, and hence the identity of the complementary base that serve as a template in the target polynucleotide (Figures 3A-3B and Column 10, line 66 to Column 11, line 34);

e) repeating steps c)-d) with a labeled further nucleotide, the same or different from the first labeled nucleotide, whereby the labeled further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer (Figures 3A-3B and Column 10, line 66 to Column 11, line 34).

Livak et al teach a method wherein the label is a fluorescent label, radiolabel or non-optical signal (Column 12, lines 54-62 and Column 5, lines 43-54).

Livak et al teach a method wherein the substrate is glass and the surface is coated with a polyelectrolyte multilayer terminated with a polyanion (Column 8, lines 19-42).

Livak et al do not teach the method wherein the fraction of the first nucleotide and the further nucleotide are less than 0.01%.

However, it is *prima facie* obvious that selection of the specific fraction of the first nucleotide and the further nucleotide represents routine optimization with regard to analyzing a target polynucleotide which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific fraction of the first nucleotide and the further nucleotide were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Livak et al do not teach the method wherein the synthesis channel is formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate.

Effenhauser et al. teach the method wherein the synthesis channel is formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate (Abstract and Figure 1 and Experimental Section).

Livak et al do not teach the method wherein the cross section of the synthesis channel has a linear dimension of less than 100 micrometer x 100 micrometer.

Effenhauser et al. teach the method wherein the cross section of the synthesis channel has a linear dimension of less than 100 micrometer x 100 micrometer (Figure 2 and Experimental Section, Fabrication of the Silicone Microchip Devices Subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the synthesis channel formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate of Effenhauser et al. into the method of Livak et al., since Effenhauser et al. state, "A simple and inexpensive molding procedure has been successfully demonstrated to allow for the fabrication of chip-based microfluidic devices. Relief structures on the silicone master are truly reproduced on the micrometer scale. The flat surfaces adhere without bonding procedures to a variety of smooth substrates, thus forming closed microchannel systems (Page 3457, Column 1, Conclusions Section, First three sentences)." Further motivation is provided by Effenhauser et al as Effenhauser et al state, "The combination of electrokinetic control of picoliter sample volumes and single-molecule detection can result in a novel tool for the manipulation of single molecular objects in solution, an emerging technology with far-reaching consequences in, for example, molecular diagnostics (Page 3457, Column 2, Conclusions Section, Last sentence)". By employing scientific reasoning, an ordinary artisan would have combined and substituted the flexible silicone microdevices of Effenhauser et al. into the method of Livak et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the synthesis channel formed by bonding a microfluidic chip

fabricated with an elastomeric material to a flat substrate of Effenhauser et al. into the method of Livak et al. in order to achieve the express advantages , as noted by Effenhauser et al., of a novel tool for the manipulation of single molecular objects in solution, an emerging technology with far-reaching consequences in, for example, molecular diagnostics.

Livak et al. in view of Effenhauser et al do not teach a multilayer elastomeric material.

Gilbert et al. teaches a multilayer elastomeric material (Figures 1a, 1b, 2, 10-11, and Column 11, line 16 to Column 12, line 38).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a multilayer elastomeric material of Gilbert et al. into the method of Livak et al. in view of Effenhauser et al, since Gilbert et al. states, "The unique properties and advantages of the multilayer optical film provides an opportunity to design highly-efficient backlight systems which exhibit low absorption losses when compared to known backlight systems (Column 2, lines 4-7)". Further motivation is provided by Gilbert et al. as Gilbert et al. states, "The indices of refraction of the layers in the multilayer stack can be manipulated and tailored to produce the desired optical properties (Column 2, lines 54-56)". By employing scientific reasoning, an ordinary artisan would have combined and substituted a multilayer elastomeric material of Gilbert et al. into the method of Livak et al. in view of Effenhauser et al, in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a multilayer elastomeric material of Gilbert et al. into the method of Livak et al. in view of Effenhauser et al, in order to

achieve the express advantages , as noted by Gilbert et al., of unique properties and advantages of the multilayer optical film that provides an opportunity to design highly-efficient backlight systems which exhibit low absorption losses when compared to known backlight systems and of the multilayer stack, having high reflectivity for both s and p polarized light over a wide bandwidth, and over a wide range of angles, in which the indices of refraction of the layers can be manipulated and tailored to produce the desired optical properties.

4. Claim 12 is rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Koster (U.S. Patent 6,225,567 B1) (May 1, 2001).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al further in view of Gilbert et al. do not teach the method wherein the elastomeric material is RTV silicone.

Kester teaches the method wherein the elastomeric material is RTV silicone (Column 7, line 63 to column 8, line 11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the elastomeric material RTV silicone of Kester into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al., since Kester states, "Performance is improved because the elastomeric housing can conform to

irregularities in the array, particularly if it is used in conjunction with a silane surface treatment and/or a silicone RTV material (Column 8, lines 63-66)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the silicone RTV material of Kester into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the elastomeric material RTV silicone of Kester into the method of Livak et al. in view of Effenhauser et al. further in view of Gilbert et al. in order to achieve the express advantages, as noted by Kester, of a novel silione material that provides improved performance because the elastomeric housing can conform to irregularities in the array.

5. Claims 22, 24, and 25 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Williams (U.S. Patent 6,232,075 B1) (May 15, 2001).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al further in view of Gilbert et al. do not teach the method wherein the pyrophosphate release is detected with an enzymatic reaction.

Williams teaches the method wherein the pyrophosphate release is detected with an enzymatic reaction.(Figure 1B and Column 5, line 55 to column 6, line 22).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al further in view of Gilbert et al., since Williams states, "The present invention provides a heterogeneous assay for the detection of pyrophosphate. The detection of pyrophosphate is advantageous in a number of biological reactions (Column 5, lines 55-58)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al further in view of Gilbert et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al further in view of Gilbert et al. in order to achieve the express advantages, as noted by Williams, of an invention that provides a heterogeneous assay for the detection of pyrophosphate advantageous in a number of biological reactions.

6. Claim 23 is rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Williams (U.S. Patent 6,232,075 B1) (May 15, 2001) further in view of Koster (U.S. Patent 6,140,053) (October 31, 2000).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. further in view of Williams teach the method of claims 1-11, 13-22, 24-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al further in view of Gilbert et al. further in view of Williams do not teach the method wherein the pyrophosphate release is detected with mass spectrometry.

Koster teaches the method wherein pyrophosphate release is detected with mass spectrometry (Figure 10 and Column 10 , lines 30-48).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the mass spectrometry of Koster into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Williams, since Kester states, "The invention provides fast and highly accurate mass spectrometer based process for directly sequencing a target nucleic acid (Abstract)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the mass spectrometry method of Kester into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Williams in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the mass spectrometry of Koster into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Williams in order to achieve the express advantages, as noted by Koster, of an invention that provides fast and highly accurate mass spectrometer based process for directly sequencing a target nucleic acid.

7. Claim 29 is rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al further in view of Gilbert et al. do not teach the method wherein the polyanion bears pendant carboxylic acid groups.

Clark et al. teach the method wherein the polyanion bears pendant carboxylic acid groups (Column 3, lines 32-50).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al., since Clark et al. state, "Such acrylic-modified waterborne alkyds are useful in a variety of coating compositions (Abstract, last sentence)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in

view of Effenhauser et al. further in view of Gilbert et al. in order to achieve the express advantages, as noted by Clark et al., of a novel waterborne alkyds containing pendant carboxylic acid groups useful in a variety of coating compositions.

8. Claims 30-32 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001) further in view of Batz et al. (U.S. Patent 6,225,052 B1) (May 1, 2001).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. further in view of Clark et al. teach the methods of claims 1-11, 13-21, 26-29 and 34-40 as described above.

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. further in view of Clark et al do not teach the target polynucleotide is biotinylated and surface is coated with biotin and streptavidin.

Batz et al teach the target polynucleotide is biotinylated and surface is coated with biotin and streptavidin (Figure 4 and Column 23, lines 38-52).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al., since Batz et al state, "The assay format using an immobilized probe is especially advantageous if the sample

contains further ingredients disturbing the irradiation of a detection, for example, by absorbing light in the range of the irradiation or emission wavelength (Column 23, lines 48-52)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al in order to achieve the express advantages, as noted by Batz et al, of an assay format using an immobilized probe which is especially advantageous if the sample contains further ingredients disturbing the irradiation of a detection, for example, by absorbing light in the range of the irradiation or emission wavelength.

9. Claim 33 is rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Gilbert et al. (U.S. Patent 6,368,699 B1) (April 9, 2002) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001) further in view of Batz et al. (U.S. Patent 6,225,052 B1) (May 1, 2001) further in view of Liu (U.S. Patent 6,165,694) (December 26, 2000).

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. further in view of Clark et al. further in view of Batz et al. teach the method of claims 1-11, 13-21, 26-28, 30-32 and 34-40 as described above.

Livak et al in view of Effenhauser et al. further in view of Gilbert et al. further in view of Clark et al. further in view of Batz et al do not teach the method wherein the surface is pretreated with RCA solution.

Liu teach the method wherein the surface is pretreated with RCA solution.(Column 2, lines 52-53 and Column 3, lines 46-65)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pretreatment with RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al. further in view of Batz et al., since Liu states, "Subsequently, an RCA solution is used to clean the surfaces to remove unwanted impurities (Column 2, lines 52-53)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al. further in view of Batz et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pretreatment with RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Gilbert et al. further in view of Clark et al.

further in view of Batz et al. in order to achieve the express advantages, as noted by Liu, of an RCA solution which is used to clean the surfaces to remove unwanted impurities.

Response to Amendment

10. In response to amendment, previous 103 (a) rejections are hereby withdrawn. However, new 103 (a) rejections have been provided on the basis of new art.

Response to Arguments

11. Applicant's arguments with respect to Craighead reference have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Kr. Chakrabarti

Arun Chakrabarti,

ARUN K. CHAKRABARTI
PATENT EXAMINER

Patent Examiner,

May 14, 2003